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PAPAIN

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Summary

Papain is obtained from the fruit and leaves of the carica papaya plant and contains enzymes similar to pepsin, but acts in both neutral and alkaline mediam. The potency of papain varies according to the method of preparation, and the usual grade digests about 35 times its weight of lean meat. The best grades are claimed to render soluble 200 to 300 times their weight of coagulated egg albumin in an alkaline medium. A temperature range from 60 to 90°C is favorable for the digestive process, and 65°C is regarded as the optimum temperature, with the pH at 5.0. Medically, papain has been used to prevent adhesions and sloughing in infected wounds, but allergic manifestations may occur (351a).

Meat tenderizing by the ultimate consumer is usually accomplished by sprinkling a meat cut with a powdered enzyme preparation, and a typical composition for this surface treatment contains 2% commercial papain. The most recent development in the enzymatic meat tenderization is the injection of proteolytic enzyme solutions into the vascular systems of cattle before slaughter. The vascular system effectively distributes the proteolytic enzyme throughout the tissues. Ante-mortem tenderization is now practiced on a fairly large scale by meat packers using low concentrations of specifically purified papain which is equivalent to 5 to 30 parts/million of commercial papain, based on the total weight of the animals. To avoid overtenderization, the meat must be refrigerated until used, and this ante-mortem tenderization

permits the production and sale of a much higher percentage of tender cuts from all grades of beef and particularly from the lower grades (172a).

When injected intracerebrally in mice, .03 ml of a solution containing 0.0005 g of papain/10 ml produced chronic spasms which invariably progressed to death within 7 to 10 minutes; given orally to rats, 200 to 600 mg of papain produced an analgesic and anti-inflamatory activity which was similar to acetylsalicylic acid (521, 134).

A 2% Vermizym in Ringer's solution perforated the skin of round worms within 2 to 5 hours and digested the body of the worms within 4 to 5 hours. A dose of 5 tablets, administered 5 times, at hourly intervals was effective in removing round worms from the human body but was not sufficient to totally erradicate the eggs. Oral administration of Vermizym produced little toxic effects, and the LD_{50} in mice was 12.5 to 18.5 g/kg and orally in rats, more than 10 g/kg. Intravenous injection into guinea pigs of 50 mg/kg of Vermizym killed the animals due to respiratory arrest. Intravenously, 60 mg/kg in rats caused a decrease in the erythrocyte and leukocyte counts, but oral administration to 10 g/kg did not have any effect on the erythrocyte nor leukocyte counts. The administration caused erosion and hemorrhage to the stomach and intestinal mucosa, but contact with the powder preparation or a concentrated solution of Vermizym for 1 hour did not produce marked damage to the dog stomach or intestinal

mucosa. Vermizym had a more damaging effect on the conjunctiva and the abraided skin than on the stomach and intestinal mucus membrane. The actions of Vermizym described above disappeared when the preparation is heated at 80°C for more than 5 minutes (508).

In several case reports it was found that the use of papain solutions on impactions in the esophagus resulted in death, and when studied under experimental conditions in dogs, it was revealed that there was a destruction of esophageal tissues. These results led to the public "urge of extreme caution in the use of papain solutions for treatment of meat impaction in the esophagus" (11a, 225).

Due to the digestive properties of papain, calcium oxalate and calcium ammonium phosphate stones were used to study the enzymatic dissolution of kidney stones. It was found that a solution of 100 mg of papain produced a 24 to 26% weight loss of the oxalate stones and a 56 to 62% weight loss of phosphate stones after 96 hours of incubation (276).

Inhalation of intratrachea administration of papain μg to rats, dogs and hamsters produced an emphysema which resembled that observed in humans. In the rat the lesions showed neither regression or resolution beyond the first 30 days following a 4-day exposure (288, 268, 407).

When papain was administered through the rabbit ear vein, it was observed that the permeability of the articular cartilage decreased and that the hexosamine and uronic acid content of the ear

cartilage was significantly decreased (305, 187, 59, 79).

Papain-containing solutions which came in contact with the rat salivary glands produced hypertrophy of the glands, but when administered directly into the stomach, hypertrophy was not observed indicating that the papain must come in direct contact with the gland. It was also demonstrated that papain significantly stimulated acid formation in saliva (565, 143, 161).

The gut content of the animals fed diets containing papain or fed diets in which papain was administered soon thereafter showed that papain increased the digestion of protein in the stomach (583, 18, 221).

PAPAIN

Chemical Information

I. Nomenclature

A. Common Names (351a)

Vegetable pepsin

Papase

B. Chemical Names

No chemical names were encountered in the literature searched.

C. Trade Names (11a, 351a)

Nematolyt	Airbuz
Vermizym	Summetrin
Tromasin	Caroid
Velardon	Papayotin

SL Papain type A-300, purified papain.

D. Chemical Abstracts Unique Registry Number

PM 9001-73-4

II. Empirical formula

No empirical formula was encountered in the literature searched

III. Structural Formula

No structural formula was encountered in the literature searched.

IV. Molecular Weight (533a)

20,000

27,000 ± 2,000

20,289

V. Specifications

A. Chemical

No chemical specifications were encountered in the literature searched.

B. Food grade (158a)

Assay. Not less than 6000 N.F. Units of papain activity per mg. (Note: One N.F. Unit of papain activity is the activity which releases the equivalent of 1 mcg. of tyrosine from a specified casein substrate under the conditions of the Assay, using the enzyme concentration which liberates 40 µg. of tyrosine per ml. of Standard Solution.)

Loss on drying.	Not more than 7%.
pH of a 1 in 50 solution	Between 4.8 and 6.2
Limits of impurities:	
Arsenic (as As).	Not more than 3 parts per million (0.0003%)
Heavy metals (as Pb).	Not more than 10 parts per million (0.001%).

C. Official Compendia

Food Chemical Codex

VI. Description (158a)

A. General Characteristics

It occurs as a white to light tan amorphous powder or as light brownish gray to weak reddish brown granules with a characteristic odor and taste.

B. Physical Properties

It is partially soluble in water, the solution being colorless to light yellow and somewhat opalescent. It is practically insoluble in alcohol, in chloroform, in ether and most organic solvents; slightly hydroscopic; partially soluble in glycerol.

C. Stability in Containers

Store in tight, light-resistant containers in a cool, dry place. Significant loss of activity resulted when heated to 60° for 30 minutes. Very stable at 30° between pH 5 and 7.

VII. Analytical Methods (43)

Papain

Title:	The determination of the concentration of hydrolytic enzyme solutions: -Chymotrypsin, trypsin, papain, elastase, subtilisin and acetylcholinesterase.
Principle Determination Step:	Titration
Principle Separation Techniques:	None
Principle Analytical Reagent:	p-Nitrophenyl N-Benzyloxycarbonyl-l-tyrosinate.

Moiety Measured:	Active cites
Substrate:	p-Nitrophenyl N-benzyloxcarbonyl-l-tyrosinate.

VIII. Occurrences and Levels

A. Plants

Bark of trunk, immature fruit, and leaves of Carica papaya Linne (Fam. Caricacea) 1 pound dried latex per tree per year.

B. Animals

No occurrences or levels in animals were encountered in the literature searched.

C. Synthetics

No occurrences or levels in synthetics were encountered in the literature searched.

D. Natural Inorganic Substances

No occurrences or levels in natural inorganic substances were encountered in the literature searched.

To study toxicity of intracerebrally injected papain in mice, .03 ml of a solution containing .00020, 0.00010 or 0.00005 g of papain/10 ml were administered. Within 3 to 5 minutes, there were generalized chronic spasms which invariably progressed to tonic spasms and death within 7 to 10 minutes after injection (521).

Studies using Manor Farms female rats weighing 90-140 g showed that 200 to 600 mg doses of papain have oral analgesic and anti-inflammatory activity which was not significantly different from that of acetylsalicylic acid (134).

"Vermizym", a papain preparation with enhanced anthelmintic effectiveness and stability, was studied to determine some of the parmacologic and toxicological properties. To study the in vitro digestion of pig round worms, one round worm each was placed in 30 cc of a 2% Vermizym-Ringer emulsion and was kept at 37° C. The results show that in 1 1/2 hours white erosion spots were observed on the surface of the worms, and that after 2 1/2 hours digestion of the worms proceeded rapidly. In 5 hours, the external body of the worm disappeared, but the worm was still capable of spontaneous movement. When the same procedures as described were performed using solutions of Vermizym whi h had been heated to 65°, 70°, 75°, or 80° for 5 minutes and cooled immediately to 37°, the emulsions preheated to 80° or above for 5 minutes completely lost their anthelmintic capacity. It was also found that there was a decrease in the anthelmintic effectiveness, dependent upon the preheating temperature. The changing of the

pH of a Vermizym-Ringer emulsion showed that the anthelmintic activity was completely lost at pH below 3 or above 9. When compared with papayotin, it was found that Vermizym produced perforation in the worm body in 2 to 3 hours, while within 5 hours papayotin only produced erosion of the skin (508).

Five men patients aged 27 to 58 years old, who were infested with round worms, were administered before breakfast 5 tablets of Vermizym at hourly intervals for 5 consecutive hours; round worms and round worm eggs found in the stools were collected during the following 7 days. Four of the 5 patients passed half-digested round worms in their stools, while no side affects were noted in any of the patients nor were there any abnormalities of the stools excreted (508).

Fasted male mice weighing 10 to 15 g were administered orally 0.25 to 0.75 cc/10 g of body weight of a 25 or 50% Vermizym emulsion. The LD_{50} was 12.5 to 18.7 g/kg and the symptoms observed were pilo-erection, difficulty in breathing, diarrhea, and weakness. Death was due to respiratory arrest. There was no difference in the toxicity due to the different concentrations, and animals which survived 1 to 2 days had blood in the stool, swelling, erosion, and hemorrhage of the mucus membranes of the anus. Gross autopsy revealed small hemorrhage spots of the serous membrane of the small intestines especially the jejunum, and in some it was observed that the intestinal walls had become thinner. No other distinct gross changes were observed in other organs (508).

1 to 5% solutions of Vermizym in 0.9% saline was injected into the upper leg vein of the guinea pig at a rate of 0.5 cc/minute. Two of 4 animals died after the administration of 50 mg/kg, and 4 of 5 died after the administration of 100 mg/kg and death was due to respiratory arrest. The animals were opened immediately after death, and the lungs showed marked expansion while the heart continued to beat. When the solution was preheated to 80° C for 5 minutes and injected intravenously into the guinea pig, a dose as high as 300 mg/kg failed to produce any toxic symptoms (508).

The same solution as described in the above paragraph was injected into the rat tail vein at a dose of 60 mg of Vermizym/kg. The results showed that there was a marked decrease in the number of red blood cells and white blood cells, and it was also shown that when the solution was administered orally to the rats at an equivalent of 10 g of Vermizym/kg, the rat was not killed, and the blood cell count did not decrease (508).

A rabbit eye irritation study was conducted in which 0.2 cc of a 10% or 25% Vermizym emulsion in 0.9% saline or 0.05 g of powder was applied to the conjunctiva of rabbits. One minute after the application of the appropriate solution, the eyes were washed with physiological saline, and the conjunctiva and cornea were examined at varying time intervals. The results showed the eyes to be closed, tearing, and bloodshot, with discharges; swelling or turbidity in the cornea could not be seen (508).

To the abraided and unbraided skin of rabbits 25% or 50% Vermizym emulsion in 0.9% saline were applied for a period of 1 hour. In the unbraided skin mild hemorrhagic spots were observed when treated with a 50% solution and in the skins of the braided animals 25% or 50% solutions showed blood in the solutions within several minutes after the treatment. At the end of 1 hour in the abraided animals there was a strong congestion and hemorrhage at the site of application. When the Vermizym emulsion was preheated at 80°C the symptoms were not observed (508).

When 0.3 cc of 5%, 10%, or 25% Vermizym emulsion in 0.9% saline was injected subcutaneously into the shaved backs of guinea pigs, it was found that with concentrations as low as 5% the site of injection gradually turned dark purple and became necrotic. The same changes were observed at the higher concentration but were found to be more rapid and the area involved much larger (508).

0.3 cc of a 25% Vermizym emulsion and 0.9% saline was injected into the thigh muscle of dogs and shortly after the injection the dogs refused to walk and lifted their legs expressing pain but within 3 hours they started to walk normally. With a 50% emulsion the symptoms were as above but there was also marked local swelling and the symptoms of pain did not disappear until 18 hours after the injection (508).

A 6 cm portion of the small intestines of dogs was used to study the action of Vermizym on the intestinal mucus membrane. 3 cc of a 50% Vermizym emulsion was injected into the small intestines and in some cases 1.5 g of Vermizym powder was placed inside the intestines; it

was found that in 1 hour after the application of either emulsion or powder the mucus membrane was congested and swollen and after 3 hours some dogs had detachment and erosion of the epithelium (508).

Fasted dogs were administered 5 cc of 20% Vermizym emulsion/kg to study the action on the stomach mucosa Five hours after the medication the animals were sacrificed and the stomach muscosa examined. Gross examination did not reveal any damages. Further study of the action on the stomach mucosa showed the same dose as above of Vermizym administered at 5 and 24 hours to dogs preheated with hexylresorcinol, was without affect on hexylresorcinol induced impairment (508).

5% Vermizym in 0.9% saline was injected into the leg vein of the dog at a dose which was equivalent to 40 to 50 mg/kg to study the effects on blood pressure. The results showed a marked decrease in the arterial blood pressure and a slight increase in the portal vein pressure and repeated injections into the leg vein produced tachyphylaxis (508).

Application of more than 5×10^5 of Vermizym to the guinea pig intestinal tract induced slower concentrations. Repeated treatments resulted in a gradual decrease in the degree of the drug affect on the contraction of the intestines. These affects of Vermizym continued to be observed in the presence of atrophine sulfate and neoantergan maleate. The responses as described for the guinea pig intestinal tract were also observed in the virgin rat uteri (508).

Rabbits and dogs were injected intravenously with 60 to 100 mg papain in 5 ml of vehicle and 350 to 400 mg papain in 20 ml of vehicle, respectively, to investigate the potential coagulation defect. Studies demonstrated that there was an immediate release of heparin after injection of papain, and the blood of both species became incoagulable. In rabbits the incoagulability persisted for many hours, and, in some cases, a mild disturbance of the coagulation factor was still observed 2 weeks after the injection (358).

To determine the local and general action of basic proteins, two studies were performed on rabbits, one in which 30 mg/kg of papin was administered intravenously, and one in which 50, 100, and 200 µg were injected subcutaneously. Papain, administered intravenously, produced a progressive increase in the number of leukocytes, which peaked 2 and 3 hours after injection, and returned to normal within 6 hours. When 100 mg papain was administered subcutaneously, edema, hyperemia and leukocytosis were observed within 2 1/2 hours after injection (89).

Rabbits were used to determine the role of papain in hematoporesis. Three dosage schedules were followed with doses of 50, 75, 100, and 150 mg/day, orally administered. The second group of rabbits received daily oral doses of a mixture consisting of 200 mg papain and 50 mg of ascorbic acid. After a 27-day period of medication with papain alone, the animals exhibited a stable condition of hypochromic anemia. After the 27th day papain was added to the normal diets of these rabbits, and there was regeneration of blood pigment

in all animals. It was observed that the rate of hemoglobin regeneration did not appear to be proportional to the dose of papain administered, as the response was observed in practically all dose levels. In the group in which papain and ascorbic acid was administered, it was found that at the end of 9 days of treatment the rate of hemoglobin regeneration was much higher than control. After 10 days of treatment, the hemoglobin level was increased well above the controls in groups which had received a papain, ascorbic acid, and iron mixture. The major finding in these 3 studies was that papain has a certain hematopoietic activity and that this activity is significantly greater when papain is given in association with some other factors present in the mixture (62).

Calcium oxalate and calcium ammonium stones were models used to study the enzymatic dissolution of kidney stones. The stones were placed in a solution of 10 ml urine + 100 mg of papain and the weights of the stones were determined on an analytical scale after 24, 48, 72, and 96 hours. The results show that treatment with urine-papain solution caused a 24 to 26% weight loss of the oxalate stones and a 56 to 62% weight loss of the phosphate stones after 96 hours of incubation (276).

Pigeons and isolated frog hearts were used to study the pathological changes in tissues and organs. In some pigeons, the administration of papain hastened emesis. When the isolated frog hearts were irrigated

with 1 to 2% papain, it strengthened the contractions of both auricle and ventricle by lengthening the refractory period, diminishing fibrilation and other cardiac irregularities, but it had no effect upon the amplitude of the heartbeat (5).

A case report and experimental study on dogs was reported with regard to perforation of the esophagus after the use of Caroid, a proprietary decongestant containing papain. A 27 year-old female was admitted to the hospital with an esophageal perforation. Ten days earlier, a bolus of meat had lodged in the cervical section of her esophagus. A solution of caroid had been administered to digest the meat. Twelve hours after the administration of the Caroid, the patient was found in a state of shock, exhibiting subcutaneous emphysema in the neck. Two days after hospitalization massive hemorrhage suddenly developed from the cervical mediastinotomy, and the patient died. Autopsy revealed that the walls of the common carotid artery were eroded and that approximately 2 inches of the cervical portion of the esophagus were completely destroyed. These findings suggested a study to determine the role of caroid in the digestion and perforation of the patient's esophagus. A bolus of meat was impacted into the esophagus of anesthetized dogs, and a caroid soltuion was introduced through a polyethylene catheter. Experiments with control animals demonstrated that meat alone produced no damage, but the caroid-treated animals exhibited some degree of damage to the esophageal wall, indicated by reddening of the mucosa and thickening of the wall at the side of the enlarged bolus. In addition, the lungs of each

caroid-treated dog exhibited edema which, in some instances, was sufficient to cause rapid death. "The results of these findings urge extreme caution in the use of Caroid for treatment of meat impaction in the esophagus" (11a).

After papain was used to soften and dislodge impacted meat from an esophagus, a patient suffered extensive destruction of the esophageal wall. Her physicians believed that when papain contacts a neucrotic area in the esophageal wall, it may induce further neucrosis in the adjacent tissue which, in turn, leads to extensive destruction of the esophagus and surrounding structures; therefore, they felt the use of papain is contraindicated in the treatment of impacted meat in the esophagus (225).

Fasting rat studies were done to determine the effect of the activity state of papain in in vivo activity. Milk clotting, egg digestion, and gelatin digestion were used to establish the in vivo activity of several papain preparations; these preparations were administered, along with a test meal, to rats in doses ranging from 1.25 to 20 mg. Data obtained in these studies revealed that papain increased the digestion 1.5- to 2.1-fold and that the gastric contents did not adversely effect the digestive activity of papain (221).

To determine whether papain increases the digestion of protein in vivo, young adult rats were fed a diet containing 0.5 g papain/100 g total diet for 7 to 15 minutes. The animals were sacrificed 2.5 hours after being fed the diet, and their stomach contents removed. An

analysis of these contents revealed that there was a 1.5 to 2.1 greater amount of protein digestion produced by feeding papain (18).

Mongrel dogs were fed soybean diets supplemented with 0.2% papain to determine the in vivo proteolytic activity of papain as demonstrated by nitrogen balance. The results revealed that the addition of papain to the diet significantly increased the rate of digestion of soybean protein, and that the papain addition also significantly reduced the amount of soybean protein required to maintain the dogs' nitrogen equilibrium (583).

Healthy male subjects ranging in age from 21 to 25 years who were given 7.5 mg of papain orally every half-hour to a total of 6 doses, showed a reduction of fibrin formation time but prolonged clot formation (255).

Male Sprague-Dawley rats, weighing 150 to 200 g, were exposed to an aerosolized 10% solution of papain in isotonic saline to study papain-induced emphysema during a 4-hour exposure interval. At least 2 animals were sacrificed at 0, 1, 2, 3, 4, 6, 8, 12, 19, and 24 hours and at 2, 3, 4, 14, 33, 16, and 90 days after exposure. The results demonstrated that the inhalation of papain produced pulmonary lesions which resembled centrilobuler emphysema, and these lesions showed neither regression nor resolution beyond the first 30 days following the 4-day exposure (268).

Morphological and biochemical assessment of papain-induced emphysema were conducted on 6-to 8-week-old male and female Syrian hamsters,

weighing between 90 and 120 g. 1 mg of papain/100 g of body weight was administered intratracheally to the hamsters, and animals from control and medicated groups were sacrificed at 1/2, 1, 2, 4, 6, 8, 32, hours and at 4 days. The results show that alveolar departitioning occurred quickly after a single dose of papain, and after 8 days, capillary obliteration was observed. The authors felt it important to note that a single dose of proteolytic enzyme causes collagen to disappear from the alveolar wall (288).

In a study on experimental papain-induced emphysema, mongrel dogs weighing between 24 and 69 pounds were intratracheally administered 1 or 4 injections of 1 or 2 mg papain/pound during a period ranging from 7 to 28 days. The data obtained from these studies showed that there were no significant changes in the arterial blood gas tension, acid base balance, or pulmonary resistance. However, the defusing capacity decreased and the total lung capacity, functional residual capacity, and residual volume increased, while elastic recoil decreased. Necropsy revealed that the resistance of airways smaller than 2 mm in diameter was increased, while resistance of larger airways decreased, and the condition induced by papain was similar both pathophysiologically and morphologically to human panlobular emphysema (407).

Nine-week-old albino rabbits weighing 1 kg were used to study the immunosuppressive activity of the 3a-1 fraction of papain. The results showed that when 10 mg of papain were administered intravenously (followed within 12 to 18 hours by antigen inoculations), there was a

marked immunosuppression. However, when papain was given 8 to 10 days after the antigen inoculation, normal antibody titers occurred. It was also observed that when papain inoculations preceded the antigen injections by 10 to 12 days, there was a reduction in antibody titers (101).

The effect of age and papain on certain steroid hormones was studied in reference to the permeability of articular cartilage in adolescent and adult New Zealand rabbits. A 1.5% solution of papain was injected intravenously by a constant infusion pump into the marginal ear vein at a rate which would deliver 35 mg/kg over a 15 minute interval. Comparison of results between adolescent and adult rabbits revealed that the permeability of the articular cartilage decreased the permeability index by 10.25, a 25% difference from the untreated group. Adult rabbits did not respond to the injections Further, in the adult animals, papain had no effect on the permeability of cartilage in those animals pretreated with cortisone (305).

To determine the chemical changes in rabbit aorta and ear cartilage induced by papain and calciferol, rabbits were given a 1% solution of papain intravenously on the 1st, 4th, 7th, and 10th day, or papain in conjunction with calciferol given orally for 10 consecutive days. The results showed that papain significantly lowered the hexosamine and uronic acid contents of ear cartilage, that in the papain-treated animals, there was a decrease in aortic hexosamine and uronic acid, and that when given simultaneously with calciferol, there was no effect on the extent of mineralization (187).

Male white rabbits, weighing 2 to 3 kg, were injected in the ear vein with 30 mg papain/kg to determine the effect of intravenous papain on cartilage glycosaminoglycans. One animal each was sacrificed at 0, 2, 6, 17.5, 18, 24, 48, and 72 hours and its ears removed immediately. The results showed that there was a decrease of non-sulfated and sulfated glycosaminoglycans in rabbit ear cartilage following the intravenous injection of papain with the maximum effect occurring at 24 hours (59).

New Zealand albino rabbits, weighing approximately 1 kg, were injected intravenously in the ear vein with .75 ml of a crude papain solution to determine the release of chondroitin sulfate from rabbit cartilage. Blood and urine samples were analyzed, and revealed that following the injections, blood and urine contained a mucopolysaccharide resembling chondroitin sulfate (in chemical and physical properties). Although the gross and histological changes were not described, it was stated that the time of appearance of the mucopolysaccharides closely correlated with changes in the ear and other organs of the animals (79).

A study of the relationship of serum cholesterol level, aorta cholesterol content and the degree of atherosclerosis in experimentally induced cholesterol-atherosclerosis was conducted in rabbits. The addition of papain to cis-oleic acid and cholesterol containing diets increased the serum cholesterol levels by half, and in animals fed cis-oleic acid alone the amount of cholesterol content in the aorta was increased 2-fold without evidence of severe aortic lesions (349).

Male Holtzman rats, 60 to 90 days of age, were used for 3-to 4-day studies of the taste receptors sialadenotrophic action of proteolytic enzymes. In the first series of tests, the proteolytic enzymes were administered as dietary additives and in the second series, 400 mg/day of papain were administered by medicine dropper and stomach tubing. At the end of the experiments, the submaxillary glands were removed. These studies demonstrated that the papain preparation administered by medicine dropper showed a significant increase ($p<.01$) in the weight of the glands but was not effective when administered by stomach tube. This difference suggested that papain must come into contact with the oral cavity in order to produce an effect on gland weight (565).

In another series of studies, sympathectomy (extirpation of the superior cervical ganglion) and parasympathectomy (section of the chorda tympani nerve) were performed by surgical procedures, and animals were fed for 5 days a diet which contained 1% papain by weight. Pre-ganglionic parasympathectomy resulted in a significant ($p<.01$) reduction in the weight of the ipsilateral gland, while post-ganglionic sympathectomy had only a slight effect (if any) on the ipsilateral glandular weight in control animals. The addition of papain to the diet resulted in a marked increase in the weight of the glands. In the animals having unilateral sympathectomy, the response of the ipsilateral gland to papain was markedly reduced. On the other hand, the parasympathectomized gland still maintained most of its response to papain; after

complete denervation, the response was absent. This result indicated that the maximum sialadenotrophic action can only occur if both autonomic branches are intact (565).

In another study, one week after resection of glossopharageal nerves or lingual nerves, 200 mg of papain were given twice daily to one group of rats, while in the second group, papain administration began 24 hours after the surgery. The duration of papain administration in both experiments was 3 days, and the data obtained showed that the usual increase in the weight of the glands followed the intraoral administration of papain was completely absent when the nerves were sectioned (565).

Male Long Evans and Holtzman rats, weighing between 50 and 62 g, were used to study submaxillary gland hypertrophy after diets with proteolytic enzymes. The animals were sacrificed after 12 days on a diet containing 10% papain, and it was found that the weight of the submaxillary gland was significantly decreased, and the weight of the salivary gland was increased. Histologically, the submaxillary gland showed marked enlargement of the alveoli with pale mucoid-appearing hypertrophied acinar cells, abundant PAS-staining cytoplasmic granules, and a peripherally displaced, disfigured, and hyperchromatic nucleus (143).

Saliva was utilized to study the effect of proteolytic enzymes on acid formation in mice, and it was found that papain significantly stimulated acid formation (161).

In vivo and in vitro studies were conducted on rats and/or rat tissues to determine the level and mode of activation of peptidase in liver, spleen, and kidney homogenates, and their relationship to orally-given proteases. In the in vitro studies, animals were given 200 mg of papain by stomach tube every half-hour for a period of 1 1/2 hours and were then sacrificed. Within 30 minutes after oral administration of papain, the trypsin-like activity, leucine, aminopeptidase activity and carboxypeptidase activity in the liver, spleen, and kidney were significantly elevated (254).

In a letter to the editor, it was stated that when human lymphocytes were incubated for 144 hours in a medium containing 8 to 40 μg/ml of papain, there was a higher incidence of blastic elements than found in the controls demonstrating a mitogenic action of papain (344).

The mitotic changes in liver after intraperitoneal papain protease injection were studied in male Wistar rats weighing 110 to 130 g. The animals were given single injections of enzyme solutions showing units of caseinolytic activity of 0.05, 0.1, 0.25, 0.4, and 0.6 in a volume of 0.25 ml/100 g of body weight and were sacrificed 48 hours after injection. There was a marked increase in mitotic index but no pathological alterations in the liver tissue, and observations of the kidney, heart, small intestines, and adrenal also revealed no mitotic changes (284).

During an 18-to 21-week study, it was demonstrated that the fatty liver observed in insulin-treated depancreanized dogs could be pre-

vented by the daily administration of the plant proteolytic enzyme papain (153).

In sheep, papain was found to be a successful anthelmintic against hamonchus contortus. It demonstrated some advantages over other anthelmintics as it was not toxic to the host and was administered safely to young, sick, or weak animals and to animals in advance stages of pregancy (127).

PAPAIN

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**Article to be found in summary

*Article to be found in text

PAPAIN

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